online © ML Comm
www.jkns.or.kr http://dx.doi.org/10.3340/jkns.2016.59.3.242
Print ISSN 2005-3711 On-line ISSN 1598-7876
J Korean Neurosurg Soc 59 (3) : 242-246, 2016

Pediatric Issue

Neurodevelopmental Problems in Non-Syndromic Craniosynostosis

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Craniosynostosis is the premature fusion of calvarial sutures, resulting in deformed craniofacial appearance. Hence, for a long time, it has been considered an aesthetic disorder. Fused sutures restrict growth adjacent to the suture, but compensatory skull growth occurs to accommodate the growing brain. The primary goal for the management of this craniofacial deformity has been to release the constricted skull and reform the distorted shape of the skull vault. However, the intellectual and behavioral prognosis of affected children has also been taken into consideration since the beginning of the modern era of surgical management of craniosynostosis. A growing body of literature indicates that extensive surgery, such as the whole-vault cranioplasty approach, would result in better outcomes. In addition, the age at treatment is becoming a major concern for optimal outcome in terms of cosmetic results as well as neurodevelopment. This review will discuss major concerns regarding neurodevelopmental issues and related factors.

Key Words : Craniosynostosis · Cognitive outcome · Neurodevelopment.

INTRODUCTION

Craniosynostosis is a primarily morphological problem and has been known as a possible disorder that can result in functional disability. However, a consistent association between neurodevelopmental status, optimal age for surgery, and intracranial pressure (ICP) has not been observed in isolated single suture craniosynostosis (SSC). Ongoing research and accumulating evidence suggest that the results of neurodevelopmental examination of isolated SSC children are mostly within the normal range[25]. However, the proportion of scores that are below average is greater for these children than in children with patent sutures, suggesting an elevated risk of developmental delays and further cognitive deterioration[16,23,24,25]. Neurocognitive impairments have been reported in 35−50% of school-aged children with isolated SSC[24]. Impairments in verbal short-term memory[24,50], as well as speech and/or language impairment[40] have been suggested to occur in isolated SSC patients. The detailed nature of the observed speech and language impairments was not presented in these studies, nor were data on non-verbal cognitive functioning. Therefore, it is unclear whether the impaired language skills in these children are due to their non-verbal cognitive abilities, form part of a global cognitive impairment, or are representative of specific language impairment. Nevertheless, several papers have reported memory, speech, and/or language impairment in idiopathic sagittal craniosynostosis. However, the relationship between language and cognitive function in isolated SSC was not explored until the early 2000s. Other socio-economic problems were suggested as possible causes of cognitive impairment in idiopathic craniosynostosis until the early 2000s.

A routine neurodevelopmental test is recommended for the screening of infants with isolated SSC, as has been carried out by other investigators[26,44]. This recommendation is based on a report of modest but reliable neurodevelopmental delays in the case of SSC in infants (under 24 months of age) prior to cranioplasty that cannot be attributed to maternal intelligence and family socio-economic variables[44]. Infants with isolated SSC had scores that were significantly lower on the Bayley Scales of Infant Development-II (BSID-II) and on the Mental and Psychomotor Developmental Indices (MDI and PDI) than those of unaffected

• Received : February 15, 2016 • Revised : April 5, 2016 • Accepted : April 6, 2016
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controls. MDI scores were two-thirds of a standard deviation below average, and PDI scores approximately one-third to more than a full standard deviation below the normative mean[44]. There have been reports that isolated SSC patients showed significantly worse psychomotor scores on the BSID compared to normative data[13,33]. In one large retrospective review of 214 patients (the mean age at final follow-up was 6.3 years and the median age was 5.1 years), 45% of the children had one or more speech, cognitive, and behavioral abnormal outcomes or a documented learning disability, special education placement, or identified behavioral problem, and 23% had a documented speech/language problem[6].

THE RELATIONSHIP BETWEEN DISTORTION OF SKULL AND COGNITIVE FUNCTION

The cranial vault and the underlying brain parenchyme can be notably distorted and deformed by SSC. It is reasonable to assume that there is a probable linear relationship between skull deformation or distortion, ICP, and neurocognitive impairment. Neuroanatomical changes resulting from the interaction between the growing skull and the developing brain can extend beyond the region directly beneath the fused suture[1]. The developmental trajectories of the brain are not aligned with that of skull growth. Furthermore, the morphological correlates for the brain and skull are different. The deformational stress on the cerebral cortex affects subcortical structures and also affects the overall spread throughout the brain[3,31]. With the increase in reports of cognitive impairment in SSC, there have been several studies suggesting that the occurrence of cognitive impairment is directly due to cranial deformation. Skull growth is regionally restricted and small intracranial volumes have been frequently reported[10], but brain volume in these cases is usually within[34,35] or exceeding[35] normal limits. Our recent data are consistent with these findings regarding intracranial volume. A smaller preoperative intracranial volume might suggest a low developmental score compared to the normal volume, although in most cases, the volume was not smaller than the age-matched average[25].

There is little evidence with which to assess the relationships between cognitive function and anatomical changes according to the specific type of craniosynostosis; however, among all the SSC types, children with metopic synostosis have been shown to be linked with the highest percentage of neurodevelopmental problems : in one study 4.8% of metopic SSC showed mental retardation[41], and another study described neurodevelopmental delays ranging from 15% to as high as 61%[5,15,32]. At school age, many of these problems do become apparent, because of the fact that children are positioned into more intellectually demanding surroundings, combined with higher expectancies of social interaction[22]. Shimoji et al.[42] has extensively studied metopic craniosynostosis, and has suggested that even milder forms of metopic ridging can be associated with significant developmental delay, language problems, and hyperactivity. Such neurobehavioral studies in children with metopic synostosis are precious and rare. The severity of frontal stenosis could be a strong primary predictor of poorer neurobehavioral outcomes[8]. Although some studies report no developmental effect whatsoever[19], intelligence quotient (IQ) inhibition has been reported by several groups[32,37]. Likewise, others noticed the effects largely at the level of neurodevelopmental disorders[8,14,22-24]. A similar prevalence of developmental delays is seen in unoperated (23%, milder form of metopic SSC) and operated (32%) children[8]. This report may suggest that the surgical release of skull distortion may not change the status of cognitive function. Therefore, these cognitive delays may primarily originate in the brain and might not be from skull distortion[2,3,24].

In unilateral coronal craniosynostosis, problems with intelligence, speech, learning, or behavior have been reported in 52% and 61% of children affected on the left and right sides, respectively[6]. It is reasonable to expect, in terms of impairments due to a unilaterally deformed skull, that deformities on the left side would be associated with language-based learning disorders, including developmental reading disorders, and those on the right side with nonverbal learning disorders, including problems with social perception and functioning[24].

INTRACRANIAL PRESSURE

Although there has been little evidence, ICP has been investigated as a possible cause of cognitive impairment in SCC[4]. The inconsistency in methods for measuring ICP makes the interpretation of the data extremely difficult[9,47]. Furthermore, there does not exist an age-matched standard for ICP measurements[10,39]. Therefore, defining increased ICP in pediatric patients is beyond the scope of this review. However, elevated ICP has been reported in 6% to 12% of isolated SSC[4,20,49]. Isolated SSC patients who were older than 1 year old tend to show increased ICP. Furthermore, this particular group of patients presented with lower neurodevelopmental status, and there was an inverse correlation between preoperative ICP and developmental quotient (DQ) or IQ[4]. The association of isolated SSC with intracranial hypertension is further contradicted by volumetric expectations. The volumetric calculated value of intracranial volume from CT is usually greater than normal values from unaffected age-matched controls[25,35]. Even though the patient shows lower than normal cranial volume, intracranial hypertension is not inevitable. Inversely normal or even increased cranial volume can result in elevated ICP[18,20]. In the author's experience, the measured intracranial volume in SSC patients was not lower than the age-matched average; rather, it was higher than average for most of these patients[25].

BRAIN ANOMALY AND SHAPE

There have been a series of reports about combined brain abnormalities, including SSC, Chiari malformation, corpus callo-

sum anomalies, ventriculomegaly, septum pellucidum anomalies[12,37], wide frontal subdural space with small frontal lobes[21], and cortical and subcortical differences[1-3]. Indeed, these anomalies may affect the neurodevelopment of SSC patients.

The morphology itself must be considered; although, the structure of brain has been believed normal in SSC[2]. Disrupted or malformed particular groups of brain structures may result in specific cognitive deficits[48]. Cortical connectivity can be disturbed by the distortion and deformation of major brain structures. This may affect the processing of information and result in functional disabilities. The spatial relationships among critical brain structures have been studied to retrieve the neural organization. The long boat-like shape of the skull results in narrow biparietal and occipital width and can potentially affect the dorsolateral prefrontal cortex and Sylvian fissure area[30,31]. Cranial remodeling surgery should reform and restore the normal anatomy of the cranial vault and base to meet the expectation that the shape of the brain will also be optimized[37]. Furthermore, significant changes in cognitive functioning can be evident over time based on small variations in neural organization.

Although the morphology of the brain in SSC patients may be affected regionally and globally throughout the entire cranial region, specific isolated SSC results in a certain type of brain deformation with corresponding neuropsychological impairment. However, primary brain malformation may contribute to neurodevelopmental impairment, along with secondary deformation[1-3]. Potential modifying factors such as neural plasticity, compensatory processes, behavioral adaptation, and environmental factors could intervene to abrogate possible negative effects from primary brain malformation or/and secondary deformation[17,45].

THE ROLE OF SURGICAL MANAGEMENT

Although minimally invasive approaches such as endoscopic suturectomy have been developed, extensive vault remodeling has been historically advocated for the optimal restoration of vault anatomy. Normal craniofacial development should be recovered, irrespective of whether limited strip craniectomy or more extensive cranial vault and orbital remodeling is judged to be a better method for the achievement of the primary goal in surgical management of SSC. Rapid volumetric expansion of the brain continues until 3 years of age. Furthermore, during the first year of life, the cranial volume triples that at birth. Around 90% of the adult size is reached by 6 years of age. Due to the progressive deformation of craniofacial structures during this rapid growth period, the earlier release of restricted and fused sutures is critical to recover the normal growth pattern and to minimize the adverse compensatory growth of the craniofacial skeleton and adjacent structures directed by brain development[28,37]. In isolated SSC, the relatively higher risks associated with particular types of cognitive impairment have been suggested by the fact that approximately 35% to 40% of assessed cases demonstrated some type of adverse neurodevelopmental outcome[22,27,43]. Although there remains considerable debate within the literature, early speech and language problems become evident in infants and children with sagittal synostosis, and working memory, attention, and planning may also be affected[24].

The deformed skull and probable increased ICP are considered potential causes of cognitive impairment in isolated SSC. These are two major variables to study in order to address whether cognitive skills improve after surgery, and whether cognitive skills are negatively affected when cranial surgery does not take place or is delayed[11]. Although there is little evidence that surgery either prevents or reduces the risk of neurobehavioral impairment[7], data from the authors' institute showed that the proportion of SSC patients with subnormal development was considerably reduced after surgery[25]. There were several 'unoperated cases' in the study by Boltshauser et al.[7]. The reason for no surgery in these cases may be due to their mild morphological appearance, as mentioned in the study, and relatively average school life. This report has weak points in such that it deals with a very broad age range (2.5−25.5 years old) and may contain parental report bias.

Surgical management for morphological deformity has been evident for its effects. However, there is no reasonable consensus regarding surgical restoration of deformed skull for the minimization of cognitive impairments. Whereas 40% or more of isolated SSC show the signs of delay or impairment by 3 years of age, nearly half exhibit apparent learning, developmental, or behavioral problems upon school entry[24]. Although the causality is unresolved, the age at surgery was found to be inversely related to developmental outcomes[46]. These observations indicate that cognitive impairment may be aggravated due to constriction of cranial vault growth and the resulting secondary cerebral deformation over time without surgical intervention.

Uncorrected increased ICP with hypovascularity may worsen with restricted cranial growth, which in turn adversely affects neurocognitive development[4,24,37,39]. Several studies have found no differences between patients that underwent surgery and those that did not, with regard to cognitive, speech, and language outcomes[4,22,23,50]. However, children who were older (>4 years old) at surgery tended to show four times more speech and language and/or cognitive impairment than those that were younger (<6 months of age) at surgery[50]. These data suggest that earlier surgery can prevent or improve later cognitive impairment[43]. A study by Virtanen et al.[50] reported a trend for those children who underwent early surgery (<1 month of age) to perform more favorably. In terms of morphological outcome, surgery before 6 months of age results in a more significant degree of improvement[38]. Given that the early surgical correction of unilateral coronal synostosis can result in successful outcomes with respect to cranial base deformities[29], earlier surgery may result in better neurodevelopmental outcomes as well.

AGE AS A FACTOR FOR COGNITIVE OUTCOMES

Although age has been known as a key factor for the favorable

morphological outcomes, the age for cognitive outcomes remains under consideration among prognostic factors. For syndromic craniosynostosis, 1 year of age has been suggested as a key factor for good cognitive outcomes. Early frontal release can preserve preoperative cognitive status, which is the main predictive factor[38]. So, in nonsyndromic SSC, the release of the constricted skull and brain before certain time point (for instance, 1 year or 6 months old) may be a critical prognostic factor for SSC, because SSC carries a low possibility of intrinsic brain malformation and associated anomalies. We cannot infer statistically significant associations among treatment status, age at treatment, and other outcomes of interest, because there has been no controlled study under statistical consideration[4,36,43,44]. In terms of morphological outcomes, there is a general agreement that surgical intervention at approximately 6 months of age is better than at later ages. Studies of intracranial pressure and developmental tests have suggested that surgery performed after more than 1 year may result in a worse developmental status[4,24,37,39]. Surgery performed between 6 months and 1 year after birth would be critical for better outcomes in terms of both morphology and development.

THE AUTHOR'S SERIES

In our experience[25], there are cognitive impairments in SSC. Twenty-seven single sagittal craniosynostosis patients underwent neurodevelopmental assessment during the preoperative period. Preoperative measurements demonstrated that MDI and PDI scores of 63% (n=17) and 74.1% (n=20), respectively, were within the normal range (±1 SD). Sixteen patients showed improvement in MDI and PDI following surgery. Postoperative measurements on 18 patients showed values equivalent to those of the normal population, although the preoperative MDI and PDI scores were lower than normal. Younger age (<1 year old) at surgical treatment was associated with advancement in both MDI and PDI (p<0.05). The average values from older patients (>1 year at surgery) showed no significant alteration or transitions in MDI or PDI. Thus, based on our small series at this time, surgical intervention on cognitive grounds could be a relative indication for surgical correction[25]. To address this hypothesis, a case-controlled, well-designed study to compare neuropsychological profiles as well as imaging-based analyses of brain structures, along with pre- and post-operative changes, should be performed[25].

PROBLEMS TO BE ADDRESSED

Due to the existing debate regarding neurodevelopmental problems in isolated SSC, we have several points to address and consider. There have been considerable and remarkable improvements in methods and design to study these areas. Investigations of a broader spectrum of neurodevelopment and behavioral problems, not limited to the mere presence or absence of retardation, have been performed[6,7,44]. Intelligence and development outcomes are mostly average to below average. Definite associations between SSC and mental retardation or significant global cognitive impairment have not been demonstrated. In younger SSC patients, psychomotor retardation is more likely than problems in abilities related to learning[24]. It may not be possible to correlate early motor development to subsequent cognitive problems, because the neuropsychological tests used for infants and adolescents are critically different. Neuropsychological impairments related to learning ability are becoming increasingly apparent and evident in school-age and older children with SSC[24].

CONCLUSION

Craniosynostosis is no more considered merely an aesthetic disorder, as numerous reports of neurodevelopmental outcomes are being published. Although there are many issues to be addressed and confounding variables to take into account, patients and their families are making more complex demands not only in terms of cosmetic appearance but also in terms of cognitive results. The clinician's point of view should be geared toward comprehensive management, embracing appearance as well as function.

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